Synthesis of A-ring modified steroid
Introduction:

Ring A modified steroids are known to show a marked anabolic and androgenic effect. From these observations it was concluded that mainly steric factors are involved in ring A structural requirements for the physiological activity of androgens and steroid-related compounds. Significant androgenic and myotropic activity was observed by Zanati and Wolff in modified A homo steroid systems. In a recent publication it has been shown that the A and B ring modified homoanalogues are found to be potent inhibitor of prostatic hyperplasia (BPH). The modified A & B ring homoanalogues decreases inter prostatic levels of DHT and cause a reduction in prostat size.

Homologation of steroid compounds by chemical transformations from the lead compounds shows regularities of increase and decrease in biological activity. For many series of compounds, lengthening of saturated carbon side chain and ring size from one to nine atoms produces an increase in pharmacological effects. Knowledge of the bioactive conformation permit the chemist to modify analogues constructively to produce novel structures that are potent and specific. Quantitative structure activity relations (QSAR), pharmacophore or receptor mapping, and more recent 3D QSAR methods, such as CoMFA, have emerged to aid in the discovery of the bioactive conformation and advances the analogue design process.

SYNTHESIS OF A-RING MODIFIED STEROID, A REVIEW:

The expansion of a cyclic ketone of the steroidal system to the homoanalogous conjugated ketone (homologation reaction) is an important reaction in steroidal systems which culminated several synthesis in this respective field. Most of the reported synthetic routes to the homo keto steroids either involve carbene addition to the enol ether or enol acetate derived from the parent ketone, followed by ring opening or diazomethane addition to the parent ketone following by rearrangements of the bonds. We have reviewed here the homologation reaction carried out by diazomethane addition, Tiffeneau-Demjanov homologation of 5α-3-oxo steroids and the difluoro carbene chemistry to homologation reaction in steroidal systems, in recent years.
Jones and Price's approach:

The detail results of studies on diazomethane homologation of ring A of 3-oxo steroids [1] (up to seven membered) have been published by Jones and Price[12]. The comparative diazomethane and Tiffeneau Demjanov homologation reactions were carried out by them on 5α-3-oxo steroids (1) with polar (OH) (1a) and non polar (CₖH₇) C-17β (1b) substituents. The sequence of reactions they performed were identical for both series of compounds and are summarized in scheme-I.

Jones and Price showed that homologations of 17β hydroxy 5α-androstan-3-one (1a) and 5α-cholestane-3-one (1b) by diazomethane take place via the equatorial approach at the C-3-CO group yielding the intermediate (4) and (5) which on rearrangement produced their desired seven membered A-homo steroids, A-homo-3-one (2) and A-homo-4-one (3) in the subsequent homologation reaction as a mixture.

In order to carry out the Tiffeneau Demjanov homologation reaction they took the same series of starting materials, compounds (1). Treatment of the 17β-hydroxy ketone (1a) with potassium cyanide in acetic acid, followed by acetylation, yielded a mixture of the epimeric cyanohydrin acetates (6c) and (10c) in which the axial cyanohydrin derivative predominated to the extent of ~8:1. Reduction of the purified cyanohydrin acetates (8c) and (10c) with LiAlH₄ gave the corresponding hydroxy amino methyl compounds (7a) and (11a) respectively which were difficult to purify and they therefore directly converted it to the more easily handled acetonides (8a) and (12a) without purification. The latter products were further characterized as their acetate derivatives (9c) and (13c). The compounds (8a) and (12a) on treatment with NaNO₂/HOAc gave a mixture of their desired A-homo steroid (2a) and (3a) respectively.

The synthetic operations followed above for the C-17β hydroxy compound (1a) were then repeated by them again in the cholestane series (1b) and the C-3 epimeric Tiffeneau Demjanov intermediates (7b) and (8b), from which (11b) and (12b) were obtained without difficulty.

Jones and Price concluded that the preferential equatorial approach of diazomethane to the 3-carbonyl carbon was preferred, this was shown by comparing the
Scheme-I

i) CH$_2$N$_2$, ii) rearrangement; iii) KCN iv) Ac$_2$O/Py; v) LiAlH$_4$; vi) (CH$_3$)$_2$CO; vi) NaNO$_2$/HOAc; viii) Ac$_2$O/Py
ratio of the resulting A-homo-3-ketone (2) and A homo 4-ketone (3) with the 
corresponding ratios produced from nitrous acid treatments of the acetonides of the 3β-
amino methyl-3α-hydroxy compound (7) and its epimer (11). They additionally pointed 
out that i) the nature of the 17-substituents does not affect the homologation pathway to 
any significant extent, and ii) in view of the widely differing results for both the 
diazomethane ring expansions and the Demjanov-Tiffeneau rearrangements, only the o.r.d. 
(c.d) measurement is reliable for determination of the proportion of (2) and (3), the normal 
purification and analytical techniques does not effect satisfactory separation of these 
ketones.

Pierre Crabbe's approach13:

Pierre Crabbe et al.13 investigated the chemical behaviour of difluoro 
cyclopropyl acetates generated by addition of difluoro carbene to the enol acetates of 
aliphatic, alicyclic, and aromatic ketones and the method was applied for the homologation 
sequence which can lead to α-difluoro ketones (homo steroid), α-fluro enones and 
substituted tropones, depending on the reaction conditions and steric as well as electronic 
factor. Their synthetic route (scheme-II) towards the synthesis of A homo steroid is 
shown below-

They obtained the 2,3 difluoro carbene adduct (15) from the steroidal enol 
acetate (14) by addition of difluoro carbene according to their own technique. They 
established the α configuration of the difluorocyclopropane ring by the absence of the long 
range coupling between fluorine and 19-methyl protons. Treatment of the adduct 
(15) with 2% methanolic potassium hydroxide gave exclusively the saturated A-homo 
difluoro keto steroid (16a). Similarly, the acidic cleavage of the cyclopropane ring of the 
adduct (15) with perchloric acid afforded the A-homo difluoro ketone (16b). They obtained 
the enol acetate (17) along with (18) by treating the difluoro ketone (16a) with acetic 
anhydride at reflux temperature in the presence of p-TsOH. Addition of the difluoro 
carbene to the enol acetate (18) yields the A-homo difluoro cyclopropane steroid (19a). 
The difluoro adduct (19a) on treatment with a base affords a complex mixture of products, 
and the compound (19a) on treatment with a methanolic solution of hydrochloric acid 
gives first the C-17 alcohol (19b), then the corresponding diol (19c). When they heated
the adduct (19c) with 5% hydrochloric acid-tetrahydro furan solution for 3 hr, they got the bis A-homo tetra fluoro keto steroid (20).

Scheme-II

i) CClF$_2$COONa, ii) a) 2% methanolic KOH, b) ethanolic perchloric acid, iii) $\rho$-TsOH/ Ac$_2$O, reflux, iv) methanolic HCl, v) 5% HCl/THF, 3 h.
RESULTS AND DISCUSSIONS
RESULTS AND DISCUSSION

Homologation of steroidal compounds by chemical transformation from its lead compounds shows regularities in increase and decrease of biological activity. For many series of compounds, lengthening of a saturated carbon side chain and ring size from one to nine atoms produces an increase in pharmacological effects.

After establishing the detail mechanistic aspects of our retro Henry cleavage reaction\textsuperscript{14}, we first applied this strategy for a short formal synthesis of the important biological molecule namely, \((R)-(\pm)-\alpha\)-lipoic acid (Chapter-IV), we thought of applying this reaction for synthesizing A-ring modified steroids - a class of compounds known to possess interesting physiological activities. For this purpose we conceived scheme-III, using readily available cholesterol as our starting material. We argued that the \(\alpha\)-nitro ketone (25) prepared from cholesterol (21) in four steps would give on reaction with 2-equivalents of vinyl magnesium bromide, compound (26a). Treatment of compound (26a) with anhydrous CuSO\(_4\) adsorbed on silica gel as per procedure described by Saikia \textit{et al.}\textsuperscript{14} would give the cleaved product (27) with an \(\alpha,\beta\)-unsaturated system in one end and primary nitro group in the other end. Treatment of compound (27) with a base such as Amberlyst A-21, Et\(_3\)N, DBU, DBN etc. would generate a nitronate dianion and undergo an intramolecular Michael addition to give the A ring modified steroid (28). The nitro group in the modified A ring can be removed reductively or this can be utilized for further modification.

Hydrogenation of cholesterol (21) over Pd-C in ethanol gave cholestanol (22) in 96% yield. PCC oxidation of cholestanol (22) in CH\(_2\)Cl\(_2\) at r.t. gave cholestan-3-one (23) in 93% yield. For enol acetylation of compound (23) we followed two procedures. In the first procedure enol acetylation of cholestan-3-one (23) has been done by treating cholestan-3-one (23) in acetic anhydride at reflux temperature with catalytic amount of \(p\)-TsOH according to the procedure reported by Liston \textit{et al.}\textsuperscript{15} giving compound (24) in 93% yield. In the second procedure treatment of compound (23) with Ac\(_2\)O, chlorotrimethylsilane and sodium iodide at reflux temperature (100\(^\circ\)C) for 1 hr according to the procedure reported by Sharma \textit{et al.}\textsuperscript{17} gave the enol acetate (24) in 85%
Scheme - III

i) $\text{H}_2$/Pd-C; ii) PCC/CH$_2$Cl$_2$; iii) (a) $p$-TsOH/Ac$_2$O; (b) CTMS/Ac$_2$O/Nal, $\Delta$;
iv) TFAA/CH$_2$Cl$_2$, 0°C; v) RMgX/THF/Et$_2$O, 0°C; vi) anhyd. CuSO$_4$.SiO$_2$, toluene, reflux;
vii) KF/MeOH (dry), reflux.
yield. In the second method the reaction time was drastically reduced from 6 h as in the case of the first method to 1 h.

Nitration of conformationally rigid steroidal enol acetate (24) by adding freshly generated trifluoroacetyl nitrate (TFAN) mixture to the ice cold solution of respective enol acetate (24), according to the procedure reported by Rank et al\textsuperscript{17}, gave the steroidal nitro ketone (25) in almost quantitative yield.

Our next aim was to perform the Grignard reaction of 2-nitro cholestan-3-one (25) with two equivalents of vinyl magnesium bromide to afford the corresponding nitro alcohol (26a). Treatment of two equivalents of vinyl magnesium bromide to a THF solution of 2-nitro cholestan-3-one (25) at 0\textdegree C gave a polar compound which on purification by preparative TLC (Hexane:EtOAc, 1:10) yielded a white crystalline compound, m.p. 89\textdegree C in 75% yield. It is known that treatment of organo magnesium reagent with cyclic $\alpha$-nitro keto compounds always give exclusively trans-nitro alcohols\textsuperscript{18}.

The compound (26a) showed sharp IR bands at 1540 and 3450 cm\textsuperscript{-1} indicating the presence of a -NO\textsubscript{2} and a hydroxyl group in the molecule. In the $^1$H NMR spectra, a double doublet integrating to one proton with $J = 6.2$ and $11.0$ Hz at 6.21 ppm and a double doublet integrating to one proton with $J = 9.8$ and $1.0$ Hz at 5.24 ppm indicated the presence of exocyclic double bond in the molecule. A double doublet integrating to two protons with $J = 8.6$ and $4.4$ Hz at 4.63 ppm indicated the presence of a -CHNO\textsubscript{2} proton in the molecule. A broad singlet integrating to one proton at 3.6 ppm indicated the presence of a hydroxyl group. A double doublet integrating to two protons with $J = 9.0$ and $4.45$ Hz at 2.21 ppm was assigned to the proton adjacent to vinyl and hydroxyl group. Another two singlets integrating to three protons each at 0.79 and 0.9 ppm respectively indicated the presence of C-10 and C-13 angular methyl group of the molecule. The mass spectrum of the compound (26a) showed m/z peak at 459 (M+). Based on these data, the structure of this compound has been assigned as:
Our next aim was to cleave the C-C bond between carbon atom bearing the nitro group and carbon atom bearing the vinyl and hydroxyl groups of compound (26a) by treating with the anhydrous CuSCL adsorbed on silica gel in order to obtain the open chain compound (27a) with $\alpha,\beta$-unsaturated system in one end and primary nitro group in the other end.

When compound (26a) was refluxed in anhydrous toluene with anhydrous copper sulfate adsorbed on silica gel, the intermittent TLC indicated formation of a less polar product. Usual work up of the reaction and purification of the product by preparative TLC (1:10, EtOAc:Hexane) gave a white crystalline compound which showed sharp IR band at 1550 cm$^{-1}$ indicating the presence of a nitro group in the molecule. In the $^1$H NMR spectrum, a little shift of the vinylic protons towards upfield and change of coupling constants values were also observed. The compound showed double doublet integrating to one proton with $J = 6.46$ and $10.66$ Hz at $5.83$ ppm and a double doublet integrating to two protons with $J = 10.0$ and $9.0$ Hz at $5.18$ ppm indicating the presence of an exocyclic double bond in the molecule. The interesting feature of the $^1$H NMR spectrum was that there was no clear triplet for the open chain nitro protons instead a double doublet integrating to one proton with $J = 3.54$ and $6.7$ Hz at $4.61$ ppm indicated the presence of a $\text{-CHNO}_2$ proton. Another broad singlet integrating to one proton at $3.49$ ppm indicated the presence of a hydroxyl group in the molecule. The hydroxyl peak also disappeared after D$_2$O exchange, further confirming the assignment. In the mass spectrum the compound showed peak at m/z 459. Analysis of these data led us to conclude that the C-C bond remained intact and only isomerization from trans-nitro alcohol (26a) to its cis-isomer (29a) had taken place and as such there was no retro Henry cleavage reaction.
In order to generalize our observation, we prepared a series of steroidal nitro alcohols namely, 3-methyl-2-nitro-cholestan-3-ol (26b), 3-ethyl-2-nitro-cholestan-3-ol (26c), 3-butyl-2-nitro cholestan-3-ol (26d) and 3-phenyl-2-nitro cholestan-3-ol (26e) by treating the respective organo magnesium reagents with 2-nitro cholestan-3-one (25). The IR, $^1$H NMR and mass spectral data of nitroalcohols (26b,c,d & e) are given in the Table 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR (cm$^{-1}$)</th>
<th>$^1$H NMR (ppm)</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>26(b)</td>
<td>1550, 3450</td>
<td>5.15 (dd, 1H, J = 6.0 &amp; 14.0 Hz -CHNO$_2$); 0.8 (s, 3H, CH$_3$)</td>
<td>447 (M$^+$)</td>
</tr>
<tr>
<td>26(c)</td>
<td>1550, 3450</td>
<td>4.5 (dd, 1H, J = 8.6 &amp; 4.4 Hz, -CHNO$_2$); 2.9 (br s, 1H, OH)</td>
<td>461 (M$^-$)</td>
</tr>
<tr>
<td>26(d)</td>
<td>1550, 3450</td>
<td>4.45 (dd, 1H, J = 8.4 &amp; 4.5 Hz, -CHNO$_2$)</td>
<td>489 (M$^+$) 432</td>
</tr>
<tr>
<td>26(e)</td>
<td>1540, 3450</td>
<td>7.1 (br, 5H, Ph); 4.5 (dd, 1H, J = 8.0 &amp; 6.0 Hz, -CHNO$_2$); 2.9 (br s, 1H, OH) ppm.</td>
<td>509 (M$^+$)</td>
</tr>
</tbody>
</table>

Table - 1

The synthetic operation followed above for the cleavage of C-C bond between the carbon atom bearing the nitro group and tertiary carbon atom of steroidal nitro alcohols (26b,c,d & e) were then repeated again utilizing the reagent anhydrous CuSO$_4$ adsorbed on silica gel and in each case isomerization of trans-nitro alcohols to its cis-nitro alcohols (29a, c, d & e) was only observed.
Finally, we modified our synthetic route and we tried to cleave the C-C bond between the carbon atom bearing the nitro group and carbonyl carbon atom of compound (25) with potassium fluoride as a base. Compound (25) on treatment with KF in dry methanol at reflux temperature for 8 hrs gave a gummy compound which on TLC analysis indicated the formation of a single compound. The compound on purification by column chromatography over silica gel using EtOAc: Hexane (1:10) as an eluent gave compound (30) as a gum. In the IR spectrum the compound showed two sharp IR bands at 1550 and 1725 cm\(^{-1}\) indicating the presence of a nitro group and a carbonyl group in the molecule. In the \(^1\)H NMR spectrum the compound showed a triplet integrating to two protons with \(J = 6.75\) Hz at 4.1 ppm indicated the presence of \(-\text{CH}_2\text{NO}_2\) protons. A singlet integrating to three protons at 3.5 ppm indicated the presence of a \(-\text{OCH}_3\) group in the molecule. Another two singlets each integrating to three protons each at 0.8 ppm and 0.68 ppm indicated the presence of C-13 and C-10 angular methyl groups of the steroid molecule. Based on these data, the structure of the compound (30) has been assigned as:

![Structure of compound (30)](image)

Attempts to perform a Gignard reaction with vinyl magnesium bromide on compound (30) did not give the desired product - instead there was lot of decomposition of the starting compound (30). In view of this, this scheme has been abandoned. However, attempts to cleave the desired C-C bond in compound (26a, b, c, d & e) will continue in this laboratory.
EXPERIMENTAL AND REFERENCES
**EXPERIMENTAL**

**Hydrogenation of cholesterol (21):**

5g (13 mmol) of cholesterol was dissolved in 25 ml distilled ethanol in the hydrogenation flask. To this solution, added 0.3g of 10% Palladium on charcoal and bottle was attached to the adapter of the hydrogenation apparatus. The hydrogenation was continued for a period of 6 hrs at 50-40 psi. After completion of the reaction, the material was filtered and washed with ethanol (3×30 ml). The combined filtrate was evaporated on rotavapour under reduced pressure to furnish the white crystalline product. The compound (22) was recrystallized from ethanol.

Yield = 4.8g, 12.37 mmol, 96%.

M.P = 141° C [lit. 140-142° C]

IR : v = 3300 cm⁻¹.

¹HNMR : δ = 0.78 (s, 3H, CH₃ at C-10); 0.9 (s, 3H, CH₃ at C-13), 3.5 (m, 1H, OH) ppm.

Mass : m/z = 388 (M⁺), 233.

**PCC oxidation of cholestanol (22):**

In a 100 ml round bottomed flask, 7.72g (20 mmol) of cholestanol and 25 ml of dichloromethane were placed. To this solution added 7.43g (30 mmol) of PCC at a time and the mixture was stirred at room temperature for about 1.5 hrs. After completion of the reaction, dry diethyl ether (50 ml) was added and the supernatant liquid was decanted from the black gum. The insoluble residue was washed with dry diethyl ether (3×50 ml) and becomes a black granular solid. The combined organic solution was passed through a short pad of silica gel and solvent was removed by distillation giving a yellow solid. The crude product was purified by short column chromatography on silica gel using Hexane:Ethyl acetate (10:1) as an eluent to afford the white crystalline solid (23).

Yield = 7.1g, 18.4 mmol, 93%.

M.P = 129° C [lit. 128-130° C]
Enol acetylation of 3-cholestanone (23):

**Method A:**

3-Cholestanone 3g (7.77 mmol) was added to a solution of acetic anhydride (1.6 ml, 15.4 mmol) and \( p \)-TsOH (50 mg). The solution was then refluxed on an oil bath for a period of 4 hrs. During refluxion period, acetic acid generated was removed by distillation care being taken to keep the distillation temperature below 125°C in order to avoid excessive losses of acetic anhydride. The solution was cooled to room temperature and dichloromethane (50 ml) was added, the resulting solution was washed with water (2×50 ml), 5% aqueous \( \text{Na}_2\text{CO}_3 \) (2×50 ml) and the organic layer was dried over anhydrous \( \text{Na}_2\text{SO}_4 \). The solvent was removed under reduced pressure to leave a solid residue which was purified by column chromatography on silica gel using EtOAc: Hexane (1:10) as an eluent to afford pure 3-acetoxy-cholestan-2-ene (24) as a white solid.

- **Yield** = 3.1g, 7.24 mmol, 93%.
- **M.P** = 157-159°C
- **IR** : \( \nu = 1710 \) (acetoxy, C=O) cm\(^{-1}\).
- **\( ^1\text{HNMR} \) : \( \delta = 0.69 \) (s, 3H, \( \text{CH}_3 \) at C-10); 0.78 (s, 3H, \( \text{CH}_3 \) at C-13); 1.88(s, 3H, \( \text{-OCOCH}_3 \)); 4.95 (t, 1H, \( J = 8.25 \) Hz) ppm.
- **Mass** : \( m/z = 430 \) (\( M^+ + 2 \)), 386.

**Method B:**

0.965g (2.5 mmol) of cholestan-3-one in 10.0 ml of acetic anhydride was treated with chlorotrimethylsilane 1.1 ml (10.0 mmol) and sodium iodide 1.5g (10.0 mmol). The mixture was heated to 100°C for 1 h and acetic acid generated was removed by distillation, then the reaction mixture was cooled to room temperature and 20 ml of diethyl ether was added. The organic layer was successively washed with water (3×20 ml),
5% Na₂CO₃ solution (20 ml), 5% aqueous sodium thiosulfate solution (20 ml) and finally with brine solution (20 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to furnish a yellow solid which was purified by short pad of column chromatography on silica gel using EtOAc:Hexane (1:10) as an eluent to yield the white crystalline solid (24).

Yield = 0.91g. 2.13 mmol, 85%.

Nitration of 3-acetoxy cholestan-2-ene (24):

Typically, the TFAN nitration mixture was prepared from freshly ground ammonium nitrate (80 mg) in CH₂Cl₂ (2 ml) and trifluoroacetic anhydride (1 ml) becomes homogeneous after vigorous stirring for 30 minutes at room temperature. This TFAN nitration mixture was then added dropwise (10 min) to the ice cold solution of enol acetate (0.214g, 0.5 mmol) in dichloromethane (2 ml). To assure completion of the reaction stirring was continued for another 10 minutes at 0°C. Extractive workup with CH₂Cl₂ gave quantitative yields of highly pure steroidal nitro ketone (25).

Yield = 0.214g, 0.5 mmol, 99%.

M. P = 130 [lit17 = 131-132°C].

IR : ν = 1732 (C=O), 1555 (-NO₂) cm⁻¹.

¹HNMR : δ = 0.78(s, 3H, CH₃ at C-10); 0.9(s, 3H, CH₃ at C-10); 5.21(dd, 1H, J = 6.0 (300 MHz) & 14.0 Hz, -CHNO₂) ppm.

Mass : m/z = 431(M⁺).

Grignard reaction in 2-nitro cholestanone (25):

General procedure:

To a stirred solution of Grignard reagent (2 mmol) in 50 ml of absolute ether/THF an ethereal/THF solution of 2-nitro cholestan-3-one (1 mmol) was added dropwise at 0°C. The mixture was stirred for 30 min at 0°C, then the temperature was raised to room temperature and stirring was continued for an additional 30 minutes. The mixture was then quenched by saturated ammonium chloride solution. The product was extracted with diethyl ether (3 x 50 ml) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product
was purified by preparative TLC using ethyl acetate: Hexane (10-25%) solvent system to afford the Grignard product.

a) 3-Vinyl-2-nitro cholestanol-3-ol (26a):

2-Nitro cholestan-3-one = 2.5g, 5.8 mmol
Magnesium turning = 0.278g, 11.6 mmol
Vinyl bromide = 0.87 ml, 11.6 mmol
Yield = 2.0g, 4.7 mmol, 75%
M.P = 89°C
IR : v = 1540 (-NO2), 1375, 3450 (-OH) cm⁻¹.

¹HNMR(300 MHz) : δ = 0.85 (s, 3H, CH3 at C-10); 0.9 (s, 3H, CH3 at C-13); 3.6 (s, 1H, OH); 4.63 (dd, 1H, J = 8.67 & 4.4 Hz, -CH2NO2); 5.24(dd, 1H, J = 9.8 & 1.0 Hz, =CHH); 5.45 (dd, 1H, J = 16.0 & 1.1 Hz, =CHH); 6.21(dd, 1H, J = 6.1 & 11.0 Hz, -CH=CH2) ppm.
Mass : m/z = 459(M⁺)

b) 3-Methyl-2-nitro-cholestanol-3-ol (26b):

2-Nitro cholestanone = 0.619 g, 1.44 mmol
Methyl iodide = 0.41 ml
Magnesium turning = 0.072 g
Yield = 0.50 g, 1.116 mmol, 81%
M.P = 103°C
IR : v = 1550 (-NO2); 3450 (OH) cm⁻¹.

¹HNMR : δ = 0.78 ( s, 3H, CH3 at C-10); 0.8 ( s, 3H, CH3); 0.83 ( s, 3H, CH3 at C-13); 5.15 (dd, 1H, J = 6.0 & 14.0 Hz, -CHNO2) ppm.
Mass : m/z = 447 (M⁺)

c) 3-Ethyl-2-nitro cholestan-3-ol (26c):

2-Nitro cholestan-3-one = 0.7 g (1.624 mmol)
Magnesium turning = 100 mg (4.166 mmol)
Ethyl iodide = 0.50 g (0.34 ml)
Yield = 0.540 g, 1.17 mmol, 78%
d) 3-Butyl-2-nitro cholestan-3-ol (26d):

2-Nitro cholestan-3-one = 0.5 g, 1.16 mmol.
Butyl iodide = 0.36 g
Magnesium turning = 100 mg
Yield = 0.440 g, 0.9 mmol, 78%
IR : ν = 1550, 3450 cm\(^{-1}\).
\(^1\)HNMR (300 MHz) : δ = 4.45 (dd, 1H, J = 8.6 & 4.5 Hz, -CH\(_2\)-NO\(_2\)); 2.9 (br s, 1H, OH) ppm.
Mass : m/z = 489 (M\(^+\)), 432.

e) 3-Phenyl-2-nitro cholestan-3-ol (26e):

2-Nitro cholestan-2-one = 0.51 g
Bromo benzene = 0.5338 g
Magnesium turning = 0.082 g
Yield = 0.379 g, 0.74445 mmol, 64%
IR : ν = 1540, 3450 cm\(^{-1}\).
\(^1\)HNMR (300 MHz) : δ = 0.7 (s, 3H, CH\(_3\) at C-10); 0.8 (s, 3H, CH\(_3\) at C-13); 4.1 (br s, 1H, OH); 4.55 (dd, 1H, J = 6.0 & 8.0 Hz, -CHNO\(_2\)); 7.1 (br, 5H, Ph) ppm.
General procedure for isomerization of compound (26) catalyzed by anhydrous CuSO₄·SiO₂:

The catalyst anhydrous copper(II) sulfate adsorbed on silica gel was prepared as per procedure described by Nishiguchi et al.¹⁹

A mixture of 2-nitro alcohol (26) [1 equiv.] and the catalyst anhydrous CuSO₄ adsorbed on silica gel (2-equiv.) in anhydrous benzene/toluene (25 ml/gm) was refluxed while monitoring the progress of the reaction on TLC. For workup, the catalyst was filtered off and washed with a polar solvent such as acetone. The combined filtrate was evaporated and the products were purified by chromatography (6-10%, EtOAc:Hexane) on silica gel.

a) 3-Vinyl-2-nitro cholestan-3-ol (29a):
M.P = 91°C
IR: ν = 1550 cm⁻¹.
¹HNMR: δ = 5.85 (dd, 1H, J = 10.7 & 6.5 Hz, -CH=C-); 5.17 (dd, 1H, J = 0.85 & 9.8 Hz, -OCH-); 4.62 (dd, 1H, J = 6.51 & 4.0 Hz, -CHNO₂); 3.5 (br s, 1H, OH) ppm.
Mass: m/z = 459 (M⁺).

b) 3-Methyl-2-nitro cholestan-3-ol (29b):
M.P = 102°C
IR: ν = 1550 (NO₂) cm⁻¹.
¹HNMR: δ = 4.49 (t, 1H, J = 8.6 Hz, -CHNO₂); 3.13 (s, 1H, OH) ppm.
¹³C = 12.1, 12.4, 18.7, 21.6, 22.81, 23.83, 24.15, 27.31, 27.44, 28.01, 28.18, 31.59, 35.17, 35.78, 36.15, 37.12, 39.52, 39.66, 39.74, 39.93, 40.97, 42.57, 53.79, 56.18, 56.27, 69.77, 76.44, 90.32 ppm
Mass: m/z = 447 (M⁺).

c) 3-Ethyl-2-nitro cholestan-3-ol (29c):
M.P = 90°C.
IR: ν = 1560, 1700 cm⁻¹.
Mass : m/z = 461 (M').

d) 3-Butyl-2-nitro cholestan-3-ol (29d):
IR : ν = 1550 cm⁻¹
¹HNMR : δ = 4.35 (dd, 1H, J = 6.0 & 2.0 Hz, -CHNO₂); 2.98 (s, 1H, OH) ppm

e) 3-Phenyl-2-nitro cholestan-3-ol (29e):
IR : v = 1550 cm⁻¹.
¹HNMR : δ = 7.1 (br s, 5H, Ph); 4.5 (dd, 1H, J = 6.0 & 2.0 Hz)

Cleavage of C-C bond between carbon atom bearing the nitro group and the carbon atom bearing the carbonyl group of compound (25) using KF/MeOH:

To a solution of 2-nitro cholestan-3-one (0.53g, 1.23 mmol) in absolute methanol (20 ml), potassium fluoride (0.142 g) was added at room temperature. The solution was refluxed for 8 hrs and then evaporated. The residue was then treated with water 20 ml and extracted with ethyl acetate (3×20 ml), the extracts were washed with brine (20 ml), dried over anhydrous Na₂SO₄, filtered and evaporated. The compound was obtained as a gummy residue.

Yield = 5.0 g, 1.1 mmol, 88%.
IR : ν = 1550, 1735 cm⁻¹
¹HNMR : δ = 4.1(t, 2H, J = 6.75 Hz, -CH₂NO₂); 3.5 (s, 3H, -OCH₃); 0.8 (s, 3H, CH₃ at C-13); 0.68 (s, 3H, CH₃ at C-10) ppm.
REFERENCES

   ibid (35), 3200, 1970.

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